

REMARKS

The Office communication dated November 21, 2003 states that claims 18-35 are pending in the present application, whereas the Reply under 37 C.F.R. § 1.111 filed on May 12, 2003 stated that claims 18-21, 23-26, and 30-31 were pending. The Examiner states that, for this reason, the Reply is not fully responsive to the Office Action dated February 10, 2003. Applicants respectfully point out that the Office Action dated February 10, 2003 stated that claims 18-21, 23-27, and 30-31 were pending in the present application. As such, Applicants respectfully disagree that the Reply was not fully responsive to the Office Action.

In any event, in order to avoid any further confusion as to the pending claims, Applicants cancel claims 18-35 and submit herewith a listing of claims that replaces all prior versions, and listings, of claims in the present application. These claims are numbered 36-49.

Claim 36 is supported by former claim 18 as presented in the entered Reply after Final filed on July 17, 2002 and correlates to claim 18 as presented in the Reply filed on May 12, 2003. Support for "a charge couple device for detecting emission spectra of said biological molecules" in claim 36 is also found in paragraph 0016 of the specification. Claims 37 and 38 are duplicates of former

claims 19 and 20 as presented in the entered Reply after Final filed on July 17, 2002, respectively. Claim 39 is supported by former claim 21 as presented in the entered Reply after Final filed on July 17, 2002 and correlates to claim 21 as presented in the Reply filed on May 12, 2003. Support for claim 39 is also found in paragraph 0017 of the specification. Claims 40, 41, and 42 are duplicates of former claims 22, 23, and 24, respectively, as presented in the entered Reply after Final filed on July 17, 2002. Claim 43 is supported by former claim 25 as presented in the entered Reply after Final filed on July 17, 2002, and correlates to claim 25 as presented in the Reply filed on May 12, 2003, which was amended slightly in said Reply to improve the grammar thereof. Claim 44 is a duplicate of former claim 26 as presented in the entered Reply after Final filed on July 17, 2002. Claims 45, 46, 47, and 48 are duplicates of former claims 30, 32, 34, and 35, respectively, as presented in the entered Reply after Final filed on July 17, 2002. Claim 45 is also supported by the specification in paragraph 0015; claim 46 is supported by the specification in paragraphs 0006 and 0007 (specifically, page 1, line 33 to page 2, line 2); and claims 47 and 48 are supported by the specification in paragraph 0007 (specifically, page 2, lines 4-18). Finally, claim

49 corresponds to claim 31 as presented in the Reply filed on May 12, 2003, and is supported by the specification in paragraph 0019.

No new matter is inserted into the application. The Examiner is respectfully requested to enter and consider the new claims in the application.

Request for Personal Interview

If, for any reason, the instant Supplemental Reply does not clarify all issues and place the present application in condition for allowance, Examiner Sisson is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to schedule a personal interview at the Examiner's convenience.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects the claims under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter not enabled by the specification. Applicant respectfully traverses this rejection if applied to new claims 36-49. Withdrawal of the instant rejection is respectfully requested.

Specifically, the Examiner asserts that the specification does not enable the skilled artisan to use the claimed device for

analysis of any property of any biological molecule linked to a fluorophore. Applicant respectfully disagrees. It is a well-settled tenant of patent law that an Applicant need not disclose, and preferably omits, that which is well known in the art. In re Bucher, 929 F.2d 660 (Fed. Cir. 1991).

In the instant case, methods for using a microarray for the immunoanalysis of oligonucleotides are well known in the art. As disclosed in the specification, the inventive apparatus is particularly suited for use in the Arrayed Primer Extension (APEX) assay. The APEX assay has been extensively described and details regarding the assay can be found in U.S. Patent 6,153,379 which explains how to overcome any art-recognized problems. Furthermore, several journal articles have been published describing the APEX method, including two in which the present inventor is the final author, Kurg et al. and Tönisson et al., copies of which are attached hereto. Kurg et al. in particular describes that the APEX method can be applied to any DNA target for efficient analysis of mutations and polymorphisms. Due to the prevalence and availability of details describing APEX, Applicant is not required to repeat information already known in the art.

Furthermore, the APEX method utilizes a primer extension reaction which does not rely on probes with equal T_m . Since the

APEX method utilizes a primer extension reaction, rather than a classical hybridization between a probe and a nucleic acid, the "problematic aspects of hybridization" identified by Carrico '313 (U.S. Patent 5,200,313) and relied upon by the Examiner, are not relevant to the present invention.

For these reasons, the skilled artisan would not require undue experimentation to perform the APEX assay using the inventive apparatus. Thus, the instant claims fully comply with 35 U.S.C. § 112, first paragraph. Withdrawal of the instant rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects the claims under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicant respectfully traverses the rejection if applied to new claims 36-49. Withdrawal of the instant rejection is respectfully requested.

Claim 18 (Paragraph 9 of the Office Action)

The Examiner rejects former claim 18 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, and the charge couple device. New claim 36 (which replaces former

claim 18) recites that the light beam is directed into the waveguide support. Support for this amendment is found in the first line of paragraph 0016. Thus, Applicant has provided the "essential structural cooperative relationship" between the light source and the waveguide support.

Claim 36 also recites means for directing the laser beam(s) into the edge of the waveguide support. As noted in paragraph 0016 of the specification, the means may be generated in a variety of ways, therefore, there is no "essential structural cooperative relationship" between the means for directing laser(s) and the other components recited in the claim besides that the means directs the laser beam(s). Instead, the structural cooperative relationship between the means and, for example, the light source, will depend on the type of means used. In any event, it is clear from the specification that the waveguide support is spatially situated between the light source and the charge couple device, as supported in paragraph 0019.

Claim 36 also recites a charge couple device for detecting emission spectra of said biological molecules. As noted in paragraph 0018 of the specification and as recited in the claims, the charge couple device detects the emission spectra of the biological molecules affixed to the waveguide support. Again, the

exact position of the charge couple device is not essential, provided that it is in a position to detect the emission spectra.

Finally, Applicant points out that a rejection under 35 U.S.C. § 112, second paragraph is only proper when a claim "fails to interrelate essential elements of the invention **as defined by applicant(s) in the specification...**[emphasis added]." U.S. Pat. & Trademark Off., Manual Pat. Examining Proc. § 2172.01 (8th ed. rev. 1 2003). Applicant has not disclosed in the specification that there is an "essential structural cooperative relationship" between the above components that is not recited in the instant claims, for the reasons explained above. Furthermore, the Examiner is reminded that not every claim must explicitly describe a functional or structural interrelationship between all elements in order to be patentable. "It is not essential to a patentable combination that there be interdependency between the elements of the claimed device or that all the elements operate concurrently toward the desired result." Ex parte Nolden, 149 USPQ 378, 380 (Bd. Pat. App. 1965). "A claim does not necessarily fail to comply with 35 U.S.C. § 112, second paragraph where the various elements do not function simultaneously, are not directly functionally related, do not directly intercooperate, and/or serve independent purposes." Ex parte Huber, 148 USPQ 447, 448-9 (Bd. Pat. App. 1965).

Therefore, Applicant respectfully submits that claim 36 fully complies with 35 U.S.C. § 112, second paragraph. Withdrawal of the instant rejection is respectfully requested.

Claim 19 (Paragraph 10 of the Office Action)

The Examiner rejects former claim 19 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, the charge coupling device, and the transparent hexahedron. Again, former claim 19 is canceled and replaced with claim 37. The light source, the waveguide support, means for directing the laser beam(s), and the charge couple device have been discussed above. Claim 37 is dependent on claim 36 and recites the further component of a transparent hexahedron. As clearly recited in claim 37, the transparent hexahedron is located between the light source and the waveguide support, occupies the same plane as the laser beam(s), revolves around an axis perpendicular to the laser beam(s), and directs the laser beam(s) into the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship" missing between the transparent hexahedron and the other components recited in claim 37. For this reason, withdrawal of the rejection is proper.

Claims 18 and 19 (Paragraph 11 of the Office Action)

The Examiner rejects former claims 18 and 19 for allegedly missing an "essential element." Again, claims 18 and 19 are canceled and replaced with new claims 36 and 37, respectively. In any event, the Examiner asserts that the support and cause for the hexahedron to rotate on an axis is essential, but missing, from the claims. Applicant respectfully disagrees. The support and cause for the hexahedron to rotate on an axis is not limited to any specific means, nor is the support and cause a novel component necessary for disclosure in the present application. As noted in the Declaration under 37 C.F.R. § 1.132 executed by Dr. Lewis T. Claiborne (of record), one skilled in the art can readily make and use the claimed device. The Examiner's implicit assertion that the support and cause for the hexahedron to rotate is beyond the scope of the ordinary artisan's skill to produce is clearly contradictory to Dr. Claiborne's learned opinion. Furthermore, the Examiner provides no proof or reasoning behind his assertions. The rejection is improper and should be withdrawn.

Claim 20 (Paragraph 12 of the Office Action)

The Examiner rejects former claim 20 for allegedly missing an "essential structural cooperative relationship" between the light

source, the waveguide support, the means for directing the lasers, the charge couple device, the optical wedge and the means for supporting and causing the wedge to revolve around an axis. Claim 20 is canceled and replaced with new claim 38. The light source, the waveguide support, means for directing the laser beam(s), and the charge couple device have been discussed above. Claim 38 is dependent on claim 36 and recites the further component of an optical wedge. As clearly recited in claim 38, the optical wedge is located between the light source and the waveguide support, revolves around an axis approximating the laser beam(s), and directs the laser beam(s) into the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship" missing between the optical wedge and the other components recited in claim 38. For this reason, withdrawal of the rejection is proper.

Furthermore, the support and cause for the optical wedge to revolve on an axis is not limited to any specific means, nor is the support and cause a novel component necessary for disclosure in the present application. As noted in the Declaration under 37 C.F.R. § 1.132 executed by Dr. Lewis T. Claiborne (of record), one skilled in the art can readily make and use the claimed device. The Examiner's implicit assertion that the support and cause for the

optical wedge to rotate is beyond the scope of the ordinary artisan's skill to produce is clearly contradictory to Dr. Claiborne's learned opinion. Furthermore, the Examiner provides no proof or reasoning behind his assertions. For these reasons, the rejection is improper and should be withdrawn.

Claim 21 (Paragraph 13 of the Office Action)

The Examiner rejects former claim 21 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, the charge couple device, the cylindrical lens, and the optical wedge. Claim 21 is canceled and replaced with new claim 39. Applicant respectfully disagrees with the Examiner's assertions. First of all, claim 39 recites "cylindrical lens" in line 5 rather than "optical lens." Support for "cylindrical lens" is found in paragraph 0017 of the specification.

The light source, the waveguide support, means for directing the laser beam(s), and the charge couple device have been discussed above. Claim 39 is dependent on claim 36 and recites the further component of a cylindrical lens. As clearly recited in claim 39, the cylindrical lens is located between the light source and the waveguide support, moves perpendicular to the plane of the laser

beam(s), and focuses the laser beam(s) into a shape smaller than the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship" missing between the cylindrical lens and the other components recited in claim 39. For this reason, withdrawal of the rejection is proper.

Claim 22 (Paragraph 15 of the Office Action)

The Examiner rejects former claim 22 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, the charge couple device and the mirror. Claim 22 is canceled and replaced with new claim 40. Applicant respectfully disagrees with the Examiner's assertions. The light source, the waveguide support, the means for directing the laser beam(s), and the charge couple device have been discussed above. Claim 40 is dependent on claim 36 and recites the further component of a mirror. As clearly recited in claim 40, the mirror is located adjacent to said waveguide support, and directs the laser beam into the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship"

missing between the mirror and the other components recited in claim 40. For this reason, withdrawal of the rejection is proper.

Claim 23 (Paragraph 16 of the Office Action)

The Examiner rejects former claim 23 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, and the diffraction grating. Claim 23 is canceled and replaced with new claim 41. Applicant respectfully disagrees with the Examiner's assertions. The light source, the waveguide support, and the means for directing the laser beam(s) have been discussed above. Claim 41 is dependent on claim 36 and recites the further component of a diffraction grating. As clearly recited in claim 41, the diffraction grating is located between the light source and the waveguide support, and selectively allows light of a specific wavelength to excite the fluorophores linked to the biological molecules. Thus, there is clearly no "essential structural cooperative relationship" missing between the diffraction grating and the other components recited in claim 41. For this reason, withdrawal of the rejection is proper.

Claim 24 (Paragraph 17 of the Office Action)

The Examiner rejects former claim 24 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, and the optical prism. Claim 24 is canceled and replaced with new claim 42. Applicant respectfully disagrees with the Examiner's assertions. The light source, the waveguide support, and the means for directing the laser beam(s) have been discussed above. Claim 42 is dependent on claim 36 and recites the further component of an optical prism. As clearly recited in claim 42, the optical prism is located adjacent to the waveguide support, and directs the laser beam(s) into the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship" missing between the optical prism and the other components recited in claim 42. For this reason, withdrawal of the rejection is proper.

Claim 25 (Paragraph 18 of the Office Action)

The Examiner rejects claim former 25 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, and the transparent liquid. The Examiner also states that it is

unclear what contains the liquid. Claim 25 is canceled and replaced with claim 43. Applicant respectfully disagrees with the Examiner's assertions. The light source, the waveguide support, and the means for directing the laser beam(s) have been discussed above. Claim 43 is dependent on claim 42 and recites the further component of a transparent liquid. As clearly recited in claim 43, the transparent liquid is located between the waveguide support and the optical prism, and directs the laser beam(s) into the edge of the waveguide support to effect total internal reflection. Thus, there is clearly no "essential structural cooperative relationship" missing between the transparent liquid and the other components recited in claim 43. For this reason, withdrawal of the rejection is proper.

Furthermore, the container for the transparent liquid is not limited to any specific type of container, nor is the type of container a novel component necessary for disclosure in the present application. As noted in the Declaration under 37 C.F.R. § 1.132 executed by Dr. Lewis T. Claiborne (of record), one skilled in the art can readily make and use the claimed device. The Examiner's implicit assertion that providing a container for a transparent liquid is beyond the scope of the ordinary artisan's skill to produce is clearly contradictory to Dr. Claiborne's learned

opinion. Furthermore, the Examiner provides no proof or reasoning behind his assertions. For these reasons, the rejection is improper and should be withdrawn.

Claim 26 (Paragraph 19 of the Office Action)

The Examiner rejects claim 26 for allegedly missing an "essential structural cooperative relationship" between the light source, the waveguide support, the means for directing the lasers, and the bandfilters. Claim 26 is canceled and replaced with claim 44. Applicant respectfully disagrees with the Examiner's assertions. The light source, the waveguide support, and the means for directing the laser beam(s) have been discussed above. Claim 44 is dependent on claim 36 and recites the further component of bandpass filters. As clearly recited in claim 44, the bandpass filters are located between the waveguide support and the charge coupled device, and are positioned in such a manner to receive emitted light and separate emission spectra from the fluorophores. Thus, there is clearly no "essential structural cooperative relationship" missing between the bandpass filters and the other components recited in claim 44. For this reason, withdrawal of the rejection is proper.

Claim 27 (Paragraph 20 of the Office Action)

There is no new claim corresponding to former claim 27.

Claim 31 (Paragraph 21 of the Office Action)

The Examiner rejects former claim 31 for allegedly being indefinite for failing to recite any active, positive method steps which delimit how the device is actually used. Claim 31 is canceled and replaced with new claim 49, a method claim. Thus, the instant rejection is overcome.

Rejection under 35 U.S.C. § 101

The Examiner rejects former claim 31 under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. Former claim 31 is canceled and replaced with new claim 49. Applicant respectfully traverses the rejection is applied to claim 49. Withdrawal of the instant rejection is respectfully requested.

Specifically, the Examiner asserts that former claim 31 is not a proper process claim because it does not set forth any steps in the process. Support for the APEX assay is found in paragraph 0019 of the specification. Applicant respectfully submits that claim 49 properly sets forth all necessary process steps. Thus, the instant rejection is overcome.

Applicant respectfully submits that the instant claims fully comply with 35 U.S.C. § 101. Withdrawal of the instant rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

The Examiner rejects claims 18, 20, 21, and 26 under 35 U.S.C. § 102(e) for allegedly being anticipated by Herron '274 (U.S. Patent 6,316,274 B1). Claims 18, 20, 21, and 26 are canceled. Applicant respectfully traverses the rejection is applied to any of the new claims. Withdrawal of the instant rejection are respectfully requested.

Herron '274 discloses an apparatus and method for multi-analyte homogenous fluoro-immunoassays. The present invention uses total internal reflection, instead of the conventional transversing light, in order to excite fluorophores. Herron '274 fails to disclose the use of total internal reflection. Instead, Herron '274 discloses a conventional fluorescence detector wherein light transverses through one or more filters in order to specifically excite fluorescently-labeled oligonucleotides hybridized to DNA probes bound to a glass support. As noted in the instant specification, a high optical noise results from the use of transversing light to excite fluorophores. The use of total

internal reflection, instead of the conventional transversing light, in order to excite fluorophores provides advantageous results not possible with a conventional fluorescence detector, such as that disclosed by Herron '274.

In addition, Herron '274 describes what is known in the art as a biosensor. In the method of Herron '274, capture molecules are pre-made and attached mechanically to the surface of the waveguide. The capture molecules are constructed to bind to a binding moiety present on analyte molecules. The analyte molecules are contained in a sample solution, which is reacted with the analyte molecules for binding to take place. Herron '274 discloses that capture molecules may be whole antibodies, antibody fragments, whole antigenic molecules or fragments, oligopeptides which are antigenic and/or similar in 3-dimensional conformation to an antibody-binding epitope, or receptor molecules (see, column 7, line 59 to column 8, line 30).

In contrast, in the present invention utilizes a light source which excites at least one fluorescently-labeled nucleotide. In the APEX method, for example, a polynucleotide of interest is hybridized to an array of oligonucleotide primers attached to the waveguide support to generate double-stranded oligonucleotides. The primers are extended by a sequence specific single base

polymerization reaction with the addition of fluorescently-labeled terminating nucleotides. The light source is directed into the waveguide support and excites each fluorescently-labeled nucleotide sequentially, and emission from the fluorescent nucleotide is detected with a charge couple device. Thus, the present invention identifies each target separately, whereas the device of Herron '274 is a biosensor that can only detect the general binding of capture molecules to analyte molecules, such as via a competitive immunoassay technique.

For all of the above reasons, Applicant respectfully submits that Herron '274 fails to anticipate the present invention. Withdrawal of the instant rejection is therefore respectfully requested.


Conclusion

Applicant respectfully submits that the above remarks and/or amendments address and overcome the outstanding rejections of record. The present application is now in condition for allowance. The Examiner is respectfully requested to issue a Notice of Allowance indicating that claims 36-49 are allowed.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments:

Kurg et al. Arrayed Primer Extension: Solid-Phase Four-Color DNA Resequencing and Mutation Detection Technology, *Genetic Testing*, 4(1):1-7, 2000);
Tönisson et al., Evaluating the arrayed primer extension resequencing assay of TP53 tumor suppressor gene, *PNAS*, 99(8):5503-5508, 2002.